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TIR 741-LSP-8023

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DATE

10/16/78

WORK ORDER REF:

WORK STATEMENT PARA:

NAS9-15487

REFERENCE:

SUBJECT

Study Report

Development of an Hypothesis for Simulating Anti-Orthostatic Bed Rest

This report summarizes the current progress of simulating anti-orthostatic bed rest. The Guyton model, modified by the addition of leg compartments and the effect of the gravity vector, was used to evaluate hypotheses describing leg dehydration and fluid shifts. While the study is not complete, the basic approach has been shown to be useful by identifying important mechanisms, identifying systems which need further experimental description and by assisting in the development of a general hypothesis.



(NASA-CR-160200) DEVELOPMENT OF AN  
HYPOTHESIS FOR SIMULATING ANTI-ORTHOSTATIC  
BED REST (General Electric Co.) 51 p  
HC A04/MP A01

CSSL 06S

Unclas

G3/52 22189

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## DEVELOPMENT OF AN HYPOTHESIS FOR SIMULATING ANTI-ORTHOSTATIC BED REST

J. I. Leonard, D. J. Grounds, D. G. Fitzjerrell

### INTRODUCTION

Many significant changes observed during space flight and bed rest can be attributed directly or indirectly to reactions initiated in the legs and their fluid and tissue compartments. These include: (a) the fluid shifts from vascular and extravascular compartments resulting from altered hydrostatic gradients, (b) the degradation of musculoskeletal tissue function due to reduced gravitational loading forces on the tissues themselves and their proprioceptors, and (c) during bed rest, there is an alteration in metabolic function in many body tissues and organs including the legs as a result of a reduction in physical activity. It appears that these disturbances, none of which are completely understood, are of such fundamental nature that they can affect circulatory, renal, hormonal, and metabolic function, not only in the acute state, but for much longer periods of time.

For these reasons we have determined that computer models used for the mathematical simulation of weightlessness must include explicit representation of the legs. One of our models - a pulsatile cardiovascular system capable of simulating short term stress - was originally designed with leg circulatory compartments and their control mechanisms. Recently, the Guyton model has been modified for this purpose by adding several vascular and extravascular leg elements. These models have made it theoretically possible to examine and better understand changes in fluid volumes, pressures and flows which may be occurring during gravity dependent stresses. This study will be concerned with some of the results achieved and problem areas encountered in modeling leg fluid shifts during head-down tilt and anti-orthostatic bed rest.

### Objectives and Scope of Study

Figure 1 illustrates the current effort in perspective with previous simulation studies. This chart also identifies several specific areas which will be discussed in this paper. Our immediate goal is the

# ASPECTS OF HYPOTHESIS DEVELOPMENT

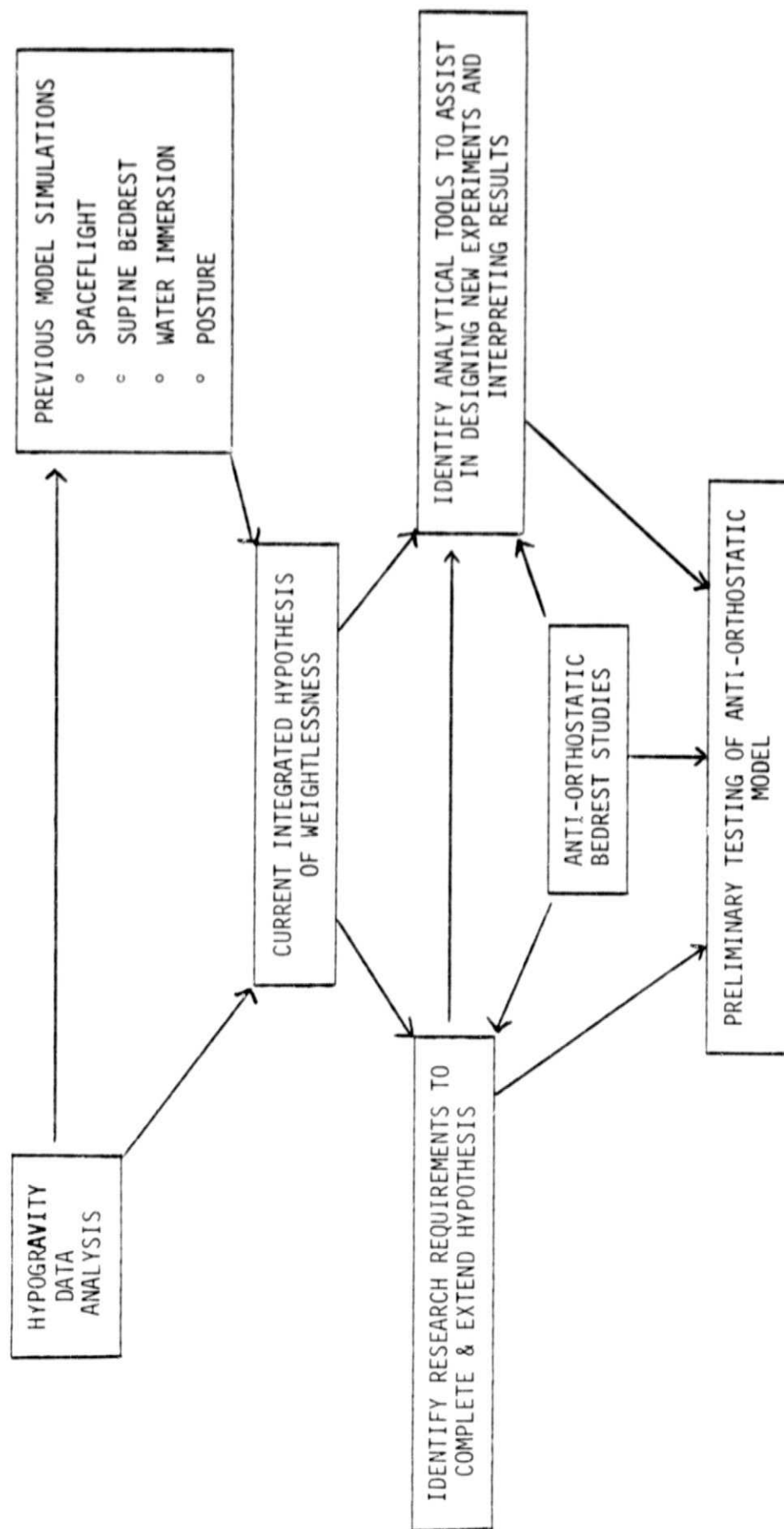
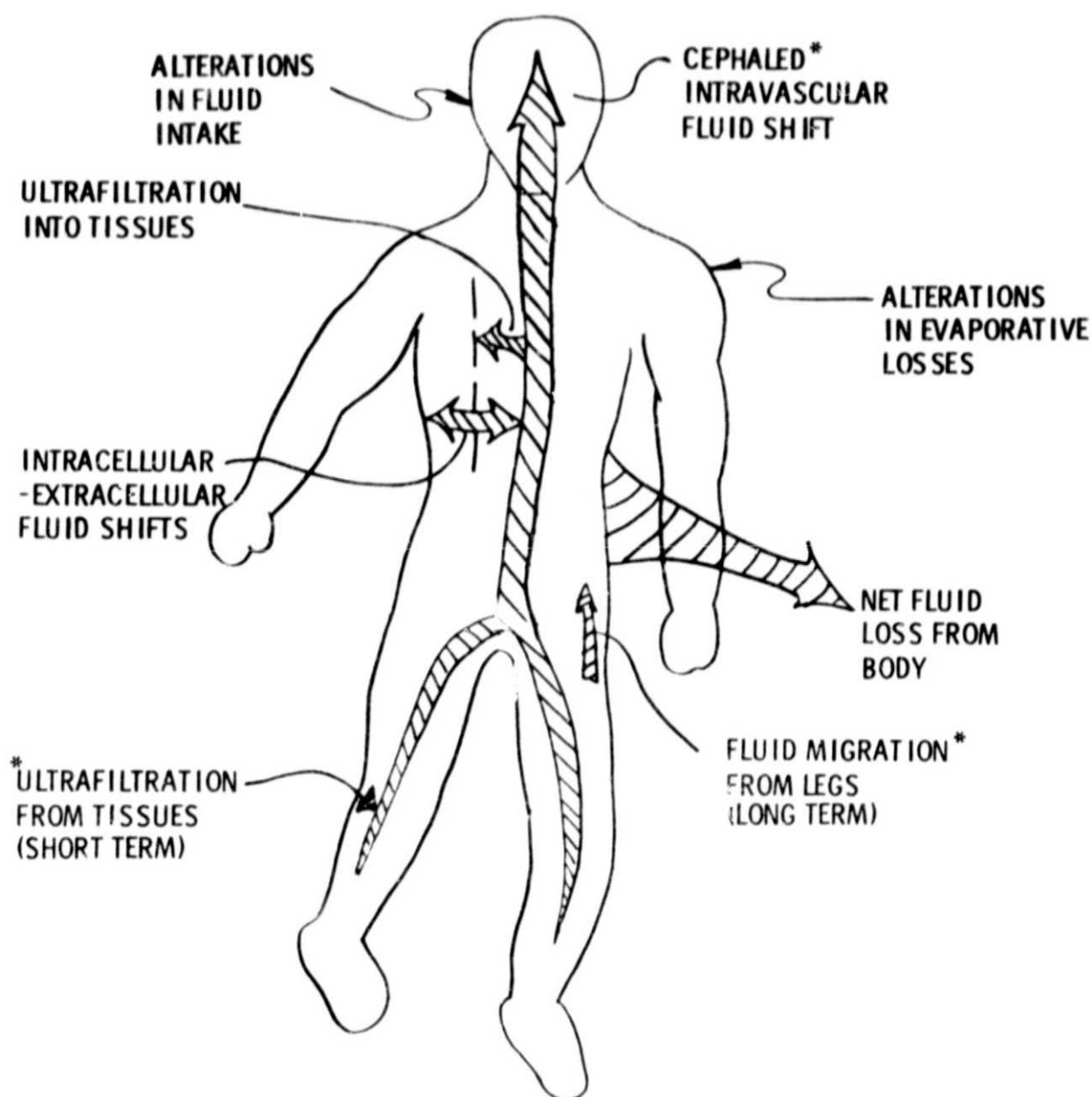


FIGURE 1

successful testing of a model which is capable of simulating the fluid, electrolyte, renal and circulatory responses to anti-orthostatic bed rest. This is a logical extension of our previous modeling efforts in simulating various forms of hypogravic stress including postural changes, water immersion, supine bed rest and space flight (Fitzjerrell, et al, 1975; Leonard & Grounds, 1977; Leonard, et al, 1977). The common physiological hypotheses that integrate these diverse stresses need to be examined and extended, if necessary, to include the responses to anti-orthostatic bed rest. At the same time our studies offer the capability of suggesting design requirements essential for gaining maximum information from new bed rest experiments.

The types of fluid shifts which we have identified as characteristic of the weightlessness response are shown in Figure 2. In previous studies we have examined the behavior of most of these shifts. In this study we have limited ourselves to those factors which are starred in Figure 2.

Our simulation of long term anti-orthostatic bed rest represents a most severe modeling challenge in that it requires a highly realistic driving force - altered gravity vector and tissue elastic forces - to shift fluid from leg compartments. During this study it became apparent that long term leg dehydration during bed rest would require a more accurate description of collapsible leg veins, nonlinear leg tissue pressure-volume relationships and the mechanisms which control their function than was heretofore available. These problems were not previously encountered in the supine model which formed the basis of our early simulations and have not yet been fully resolved. Therefore, the main objectives of this study have not yet been achieved and this effort is still actively in progress. We will limit our discussion to our approach in developing hypotheses, difficulties encountered, and recommendations for achieving realistic simulations of fluid shifts in legs during head-down bed rest for up to two weeks. Secondary effects in the hormonal, renal, and biochemical areas will not be considered at this time. In order for this discussion to be meaningful, however, we will present as background a brief review of the computer model and some unreported results of supine bed rest and space flight simulations.



**TYPES OF FLUID SHIFTS DURING WEIGHTLESSNESS SIMULATED  
BY MODIFIED CIRCULATORY, FLUID & ELECTRLYTE MODEL**

FIGURE 2

### Simulation Models

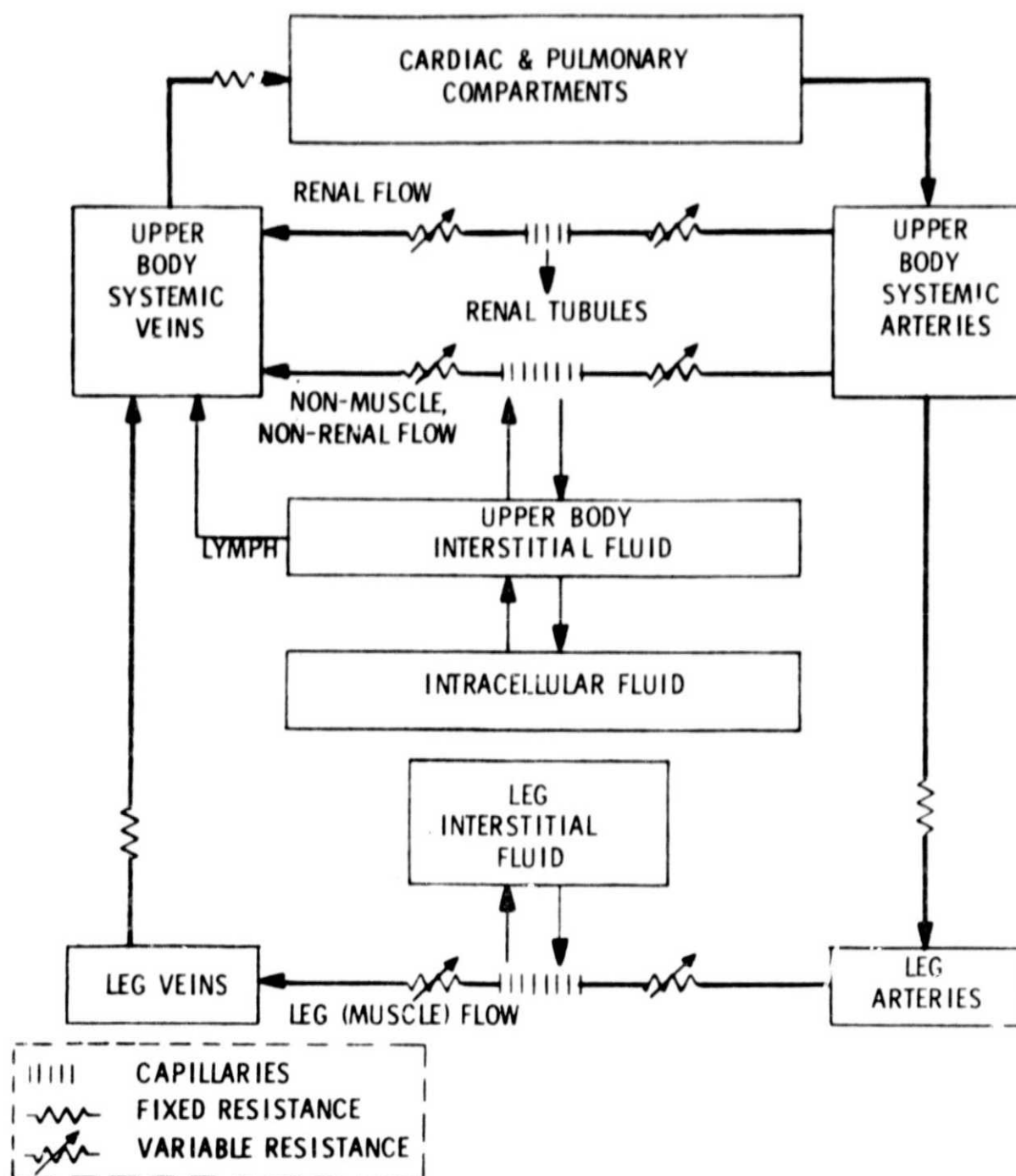
The computer simulation models we have employed as an aid in understanding the weightlessness response have been described in detail in previous presentations. In brief, they consist of models of the thermoregulatory, cardiovascular, respiratory, fluid-electrolyte and erythropoiesis systems. These models have been used both separately and in combination with each other; in the latter case, the whole-body algorithm is capable of simulating prolonged space flight, including the periodic metabolic and cardiovascular stress tests. This presentation will deal primarily with studies using the model of Guyton and reference will also be made to studies of exercise and LBNP performed with the GE pulsatile cardiovascular model (Guyton, et al, 1972; Croston & Fitzjerrell, 1974).

The Guyton model was recently modified to include leg elements in preparation of anti-orthostatic bed rest studies (Figure 3) which consists of: a) a leg arterial compartment, b) a leg venous compartment, c) a functional leg capillary bed, d) active resistance components in arteriolar and venule vessels on either side of the capillary bed, and e) a leg tissue compartment. Each of the fluid compartments are characterized by a pressure, volume, and compliance. Blood flow through the legs is maintained by a pressure gradient between arteries and veins. In addition, the capability for postural change was represented by a gravity vector acting on blood pressures in both leg vascular compartments and at the baroreceptors. This vector could assume any angle from the normally supine position.

The model of Guyton contains a blood circulatory compartment as well as interstitial and intracellular compartments, separated appropriately by elements representing capillary and cellular membranes. Control of the fluid and electrolyte components of the extracellular space is indicated by the simplified diagram of Figure 4.

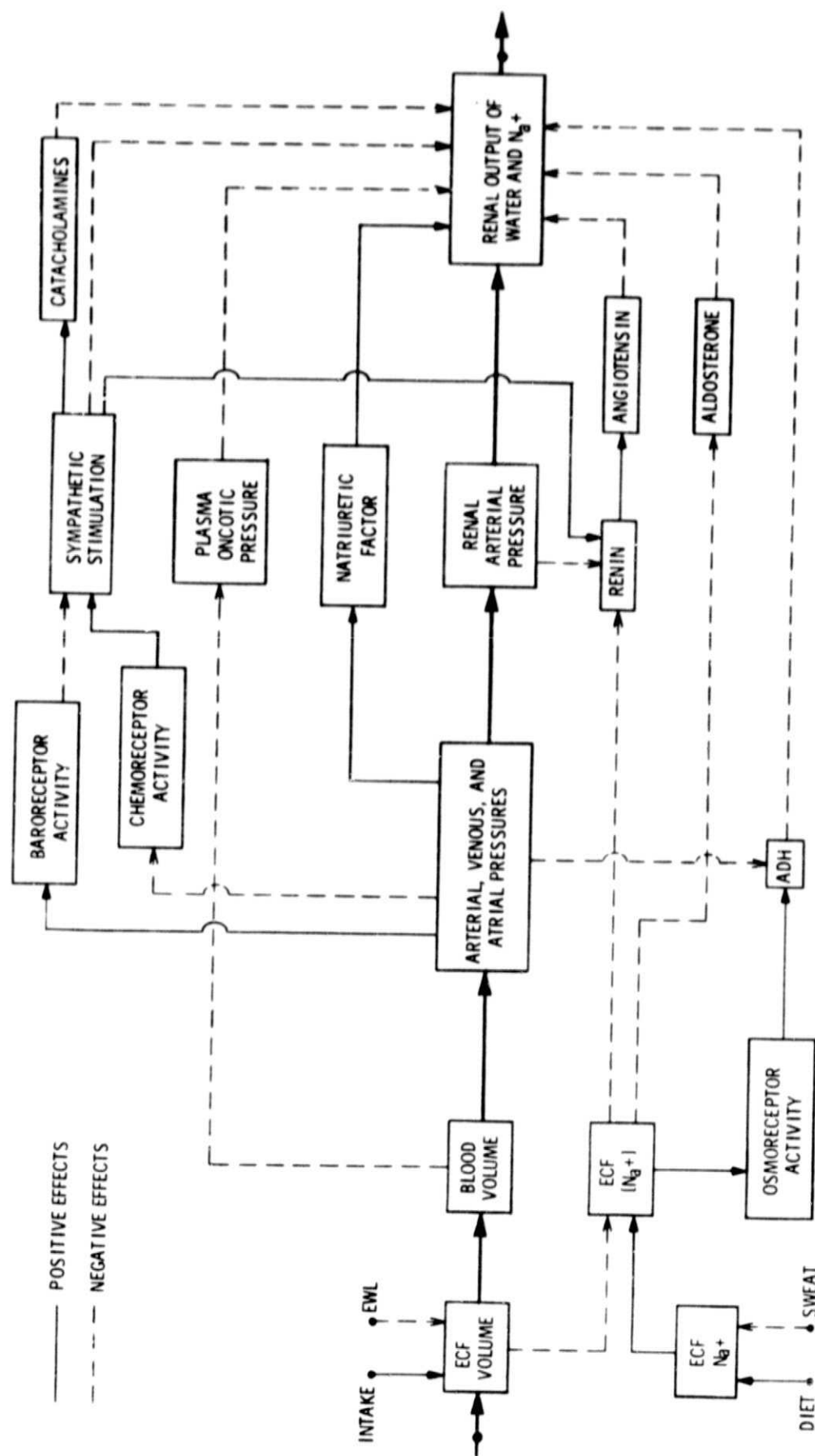
### Previous Simulations of Supine Bed Rest and Spaceflight

Previous simulations with the Guyton model demonstrated that hypervolemia of the central circulation secondary to fluid shifts from the leg compartments could reproduce a large number of the circulatory,



**CIRCULATORY AND FLUID COMPARTMENTS IN MODIFIED GRAVITY  
DEPENDENT MODEL OF CIRCULATORY, FLUID AND  
ELECTROLYTE REGULATION**

FIGURE 3



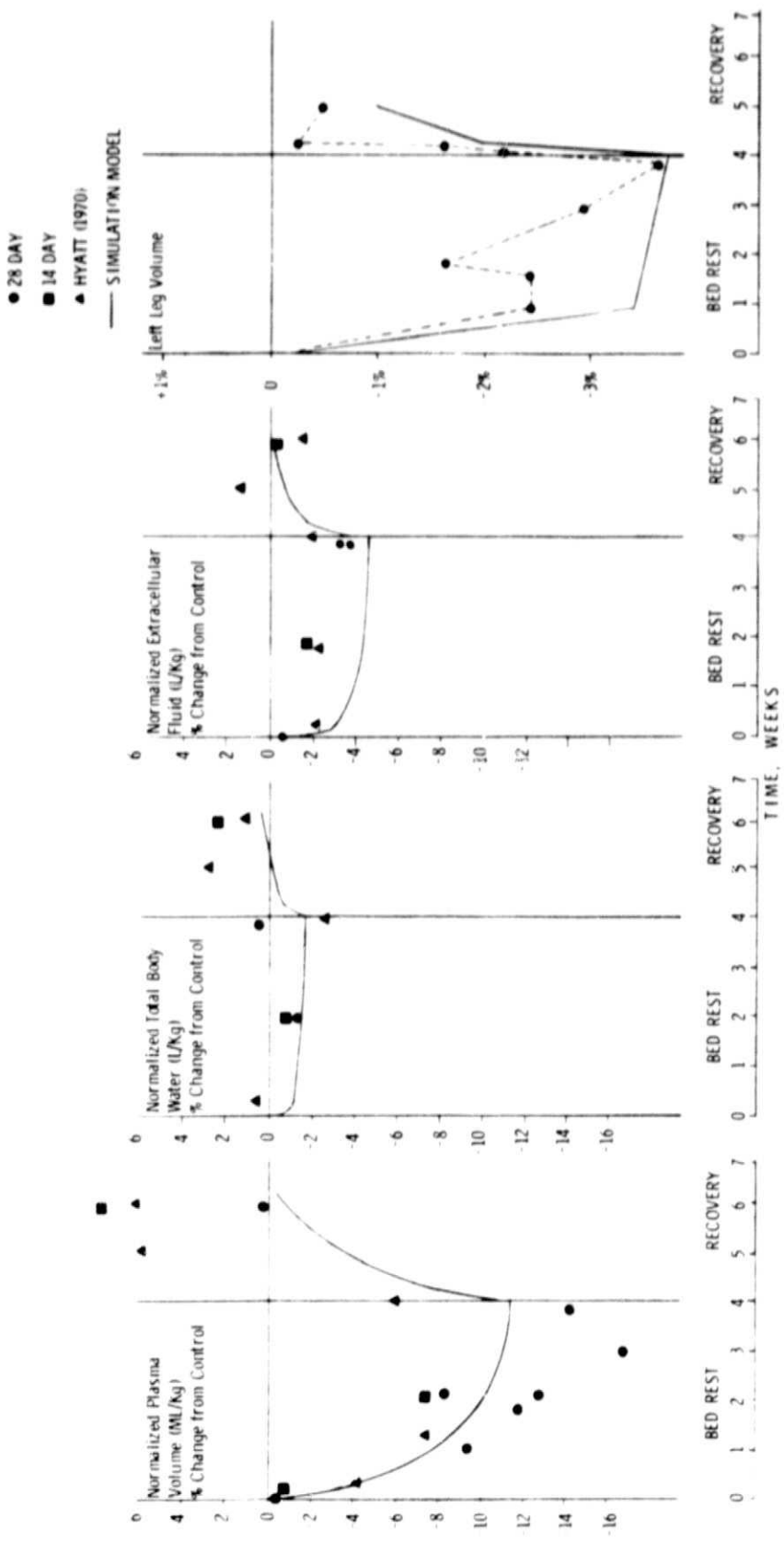
NEURAL AND HORMONAL REGULATION OF RENAL WATER AND SODIUM EXCRETION  
DUE TO EXTRACELLULAR AND CIRCULATORY DISTURBANCES

FIGURE 4

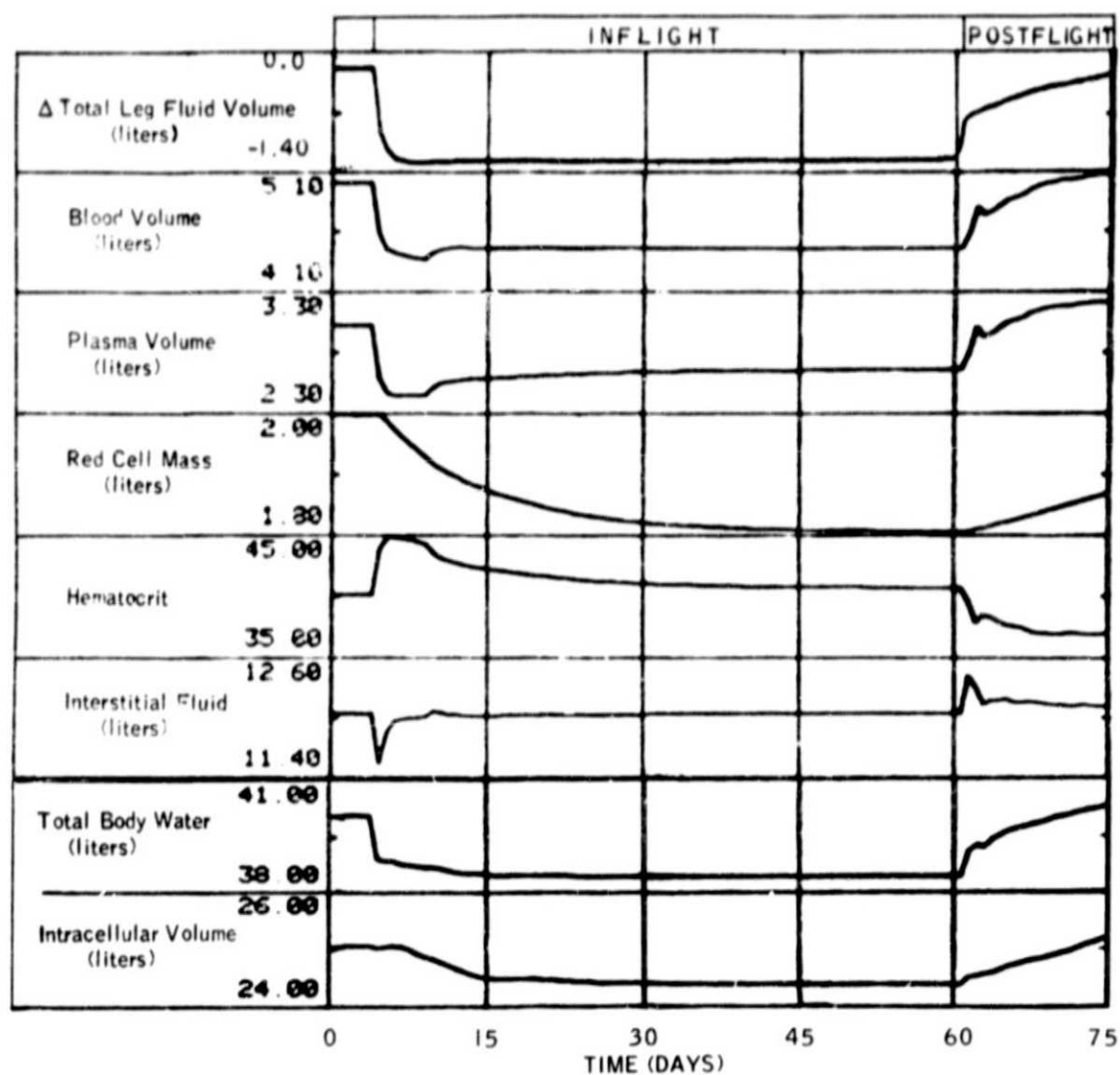
hormonal, renal, and other biochemical changes observed during acute stresses such as postural change and water immersion and longer term studies of bed rest and space flight. In addition, the combined whole-body algorithm demonstrated symptoms of degraded orthostatic and exercise function characteristic of extended bed rest deconditioning. The stress of hypogravity in these studies was simulated by forcing a predetermined amount of fluid from the appropriate leg compartments. While this initial maneuver may be considered somewhat artificial, the eventual distribution and fate of this mobilized fluid was completely under the guidance of feedback volume control elements contained in the model.

The fluid volume changes predicted by the model during four weeks of simulated bed rest are shown in Figure 5 compared to data from several bed rest studies. Figure 6 is a simulation representing the composite response of Skylab astronauts during a mean two-month mission followed by a two-week recovery. Experimentally determined dynamic changes in leg and blood volumes were used to derive fluid forcing functions for the model. Simulations were thereby accomplished which could distinguish between these two separate hypogravic conditions. Increased fidelity was achieved by including hypotheses such as reduced metabolic activity and evaporative water loss during bed rest and motion sickness anorexia during space flight. In addition, muscle atrophy and loss of intracellular minerals was accounted for by introducing a potassium loss function.

These space flight results represent the most complete and accurate hypogravic simulations achieved to date. Parameters which reflect fluid shifts and redistribution are illustrated in Figure 6. Other quantities such as electrolytes, hormonal levels and renal excretion were also successfully simulated, but are beyond the scope of this presentation and are not shown. The acute changes shown during the first five days following launch represent not only the influence of fluid shifts from the legs, but realistic reductions in fluid and mineral intake which accompanied space motion sickness. In some cases, the model predicts results which



BODY FLUID VOLUME CHANGES DURING BED REST  
FIGURE 5



SIMULATION OF COMPOSITE SKYLAB MISSION:  
 FLUID SHIFTS  
 FIGURE 6

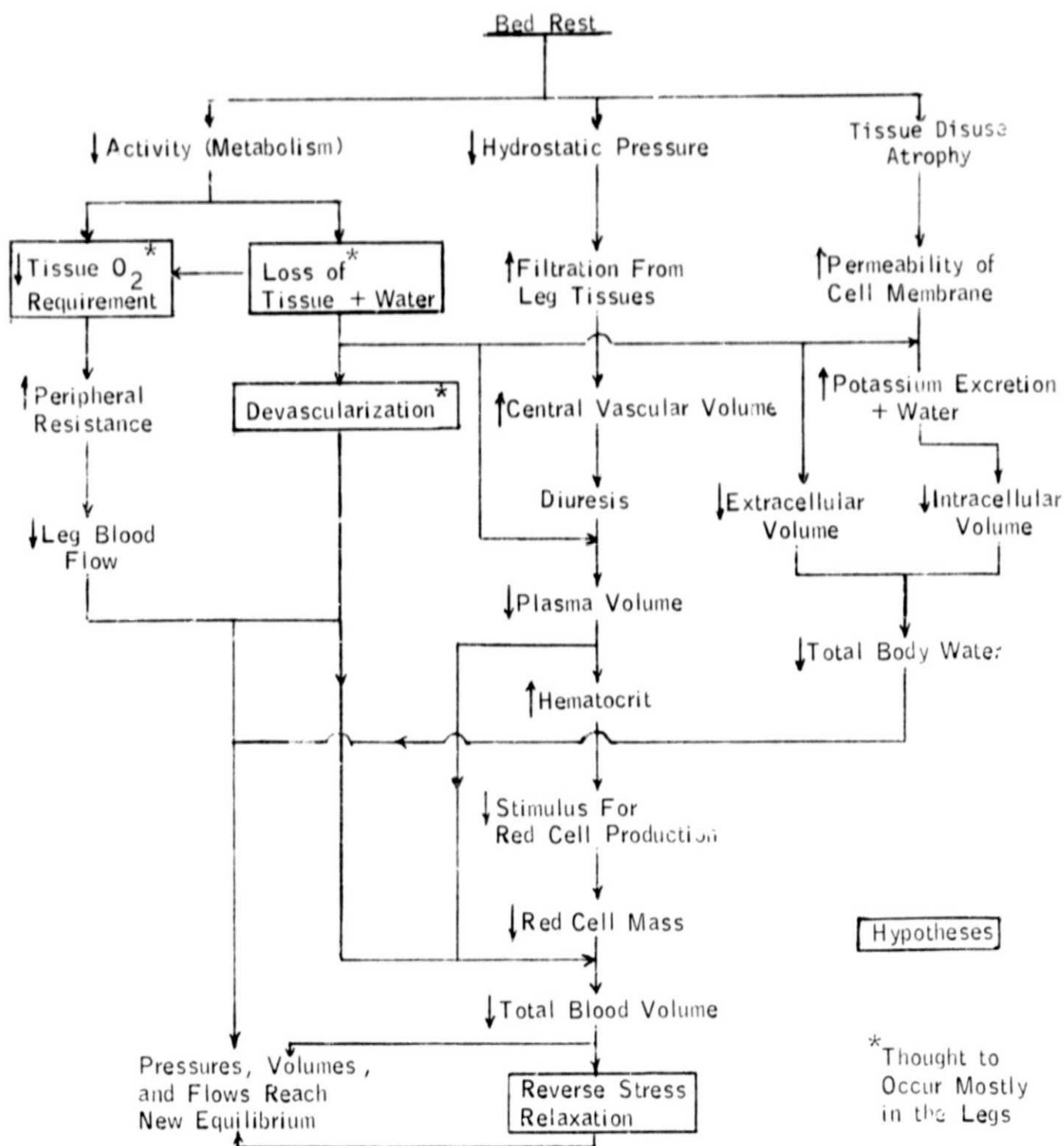
took place prior to the first inflight measurements, and these must await verification on future flights. A feature of these simulations is that the dynamic behavior of each parameter is unique and quite different from each other. Also, recovery is in general a longer process than the more acute changes following launch, consistent with postflight measurements. These dynamic properties reflect the complex interactions of feedback elements and their diverse time constants and non-linearities represented in the model. Table I summarizes a number of events simulated in these hypogravic studies all of which are generally agreed to be important elements of the weightlessness response.

A general hypothesis to account for the redistribution of fluids during bed rest is presented in Figure 7. The three primary disturbances include: a) altered hydrostatic pressure leading to leg fluid shifts and reduction in blood volume, b) altered gravity loading on muscle tissues which result in disuse atrophy (i.e. loss of intracellular water and minerals), and c) altered body metabolism represented as reduced tissue oxygen and circulatory requirements as well as reduced tissue mass. This hypothesis is based on the mechanisms in the model which become operative during hypogravic simulations. Recognizing that the model is an extremely simplified representation of the real system, this chart is only meant to be suggestive of the actual events which may be involved.

Central to this hypothesis is the reduction of hydrostatic forces in the blood column, which, coupled with the normal tissue elasticity and muscle tone of the lower body, results in headward shifts of fluid from the legs. The consequent relative central hypervolemia and stimulation of cardiopulmonary vasculature stretch receptors leads to a complex of neurohumoral responses and rapid secondary changes in the cardiovascular and renal systems. These latter pathways have been presented in detail in previous presentations and have been omitted in Figure 7. The net result, however, is a renal loss of fluid and electrolytes provided that normal food and fluid intake is maintained. As a result of these various processes, there is a significant redistribution of intracellular/extracellular and intravascular/interstitial fluid and

TABLE 1  
 PHYSIOLOGICAL EVENTS IN ZERO-G SIMULATION  
 BY WHOLE-BODY MODEL

- Fluid shifts from legs
- Redistribution of blood towards head
- Changes in blood flow and pressures
- Altered secretion of hormones: ADH, Angiotensin, Aldosterone
- Early increase in urine water, sodium and potassium
- Influence of suppressed fluid intake on acute response
- Redistribution of intracellular/extracellular fluid
- Redistribution of intravascular/interstitial fluid
- Altered sympathetic discharge to heart, vessels and kidneys
- Decreased plasma volume
- Influence of third factor on renal function
- Change in osmotic concentration of body fluids
- Increased hematocrit
- Suppressed erythrocytosis and decreased red cell mass
- Decreased body water, sodium and potassium
- Decreased orthostatic tolerance upon recovery



HYPOTHESES OF CIRCULATORY AND FLUID VOLUME  
SHIFTS DURING BED REST

FIGURE 7

electrolytes and a concomitant reduction in total body water, plasma volume and major body electrolytes. The extent of these losses appears to be self limiting and dependent in large part on the fluid volumes shifted from the legs. The loss of circulatory volume initiates compensatory mechanisms via central neurohumoral (i.e. baroreceptors, catecholamines, angiotensin, etc.) and local (i.e. flow autoregulation, stress relaxation, devascularization) processes which gradually act to retone the circulation and establish new equilibrium levels for flows, pressures and volumes. The specifics of these adaptive processes including their time course, are not well understood. The model contains many of these features, but validation has been hampered by the lack of measurements which require invasive techniques during the prolonged periods of hypogravity. Even less well understood than the circulatory adjustments are those which pertain to accommodations in the extravascular compartments. Our work does support the belief, however, that these changes are manifest not only in the weightlessness of spaceflight, but also in various forms of bed rest and water immersion. Thus, the systems analysis approach has the useful potential, currently being realized, of quantitatively integrating spaceflight results with other ground-based hypogravic studies which can be more rigorously and carefully performed.

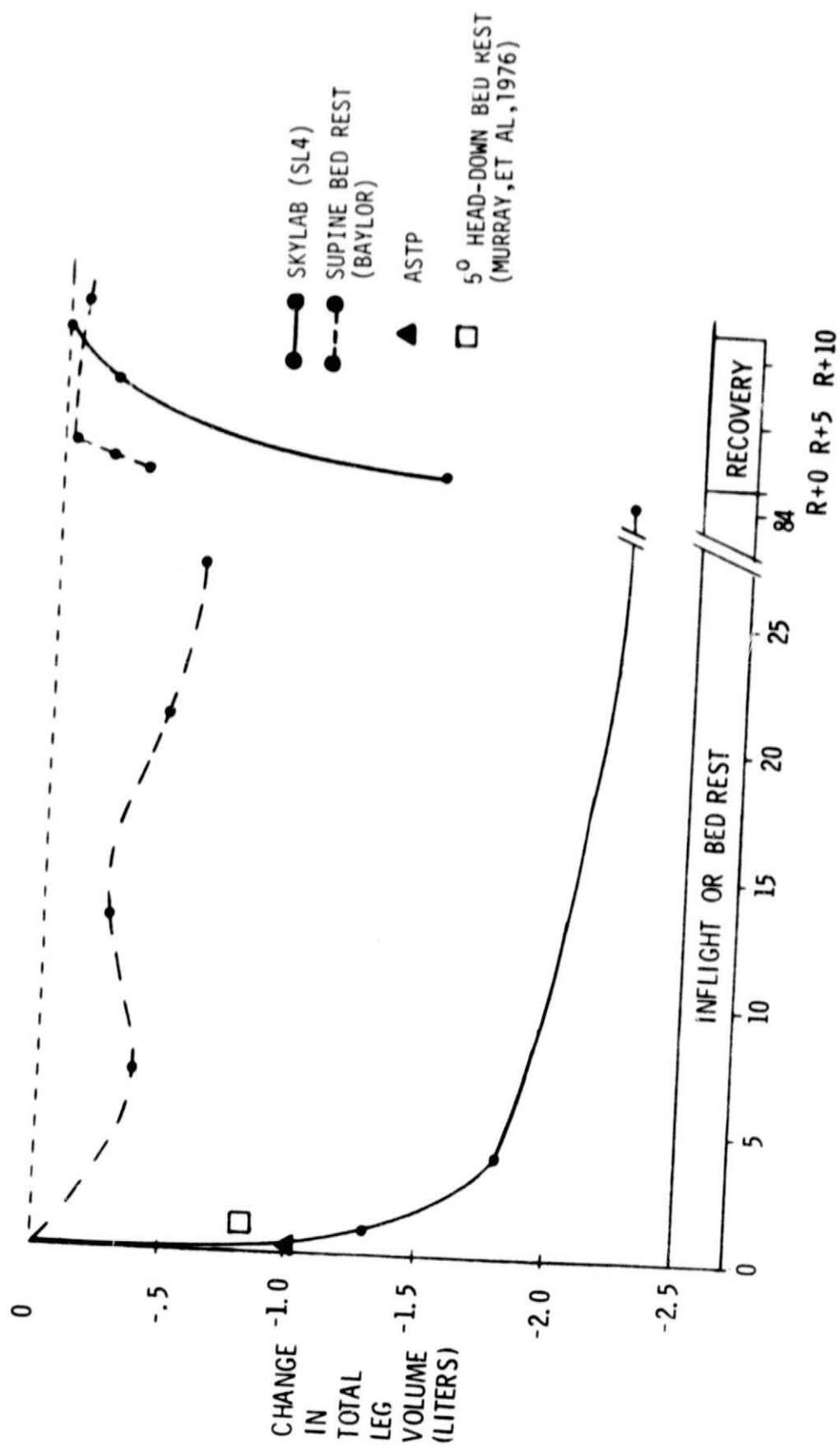
The remainder of this paper will be devoted to specific aspects of hypothesis development for simulating head-down tilt and bed rest. In the short time we have been pursuing this task, it has become evident that one of the keys to achieving a realistic simulation is a better understanding of events which occur in the legs during alterations of hydrostatic gradients. This includes the gross details of inter- and intra-compartmental fluid transport as well as the finer details of mechanisms which influence the disturbances and respond to them over prolonged time periods. The mechanisms with which we are currently concerned are those which relate to modeling collapsible veins and dehydration of extravascular tissue. These will be discussed following a brief description of leg fluid shifts during hypergravity.

## HYPOTHESIS DEVELOPMENT STUDY

### A. Fluid Shifts from the Legs

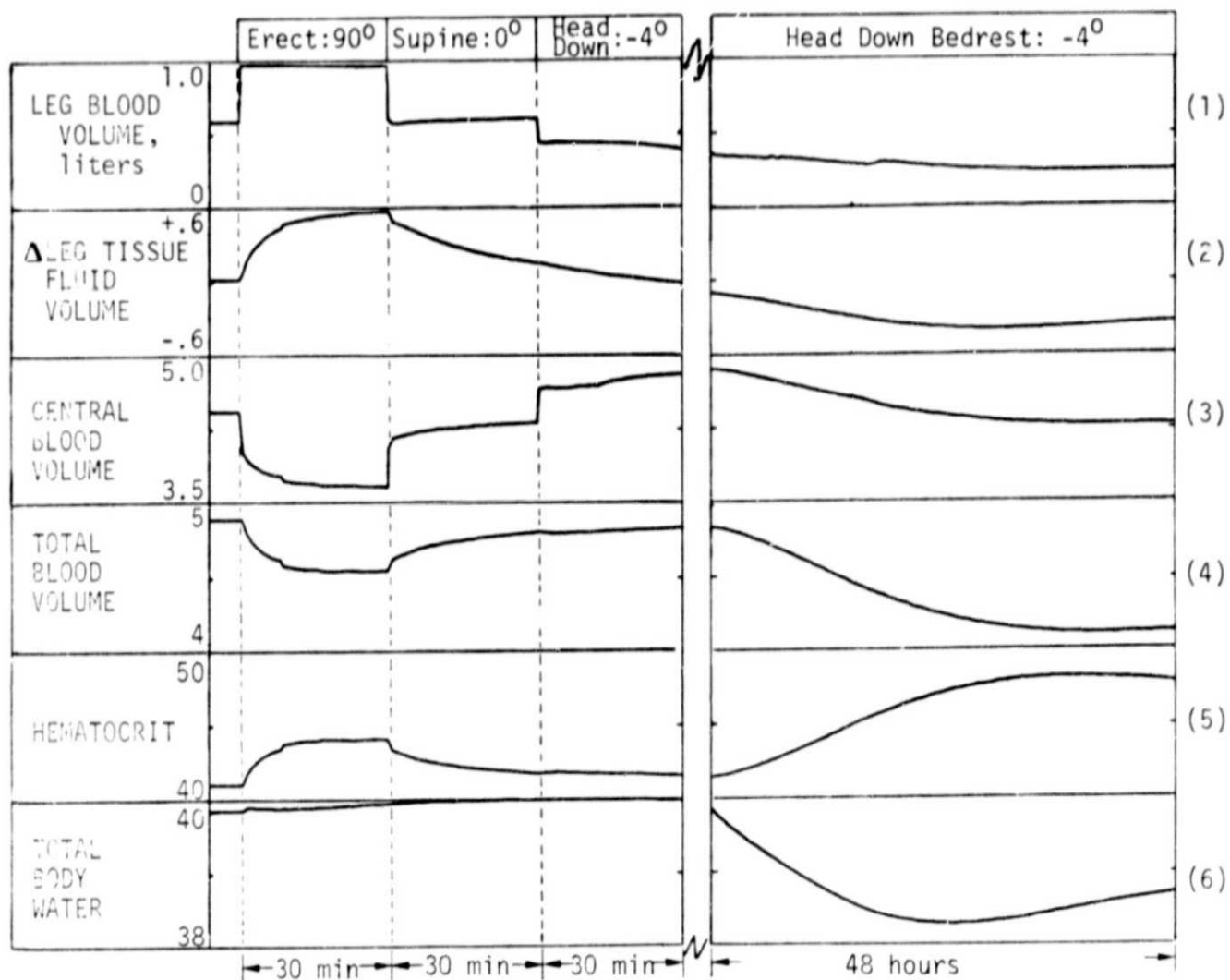
Figure 8 illustrates the magnitude of fluid transport from the legs in several different hypogravic maneuvers: spaceflight, supine bed rest, and anti-orthostatic bed rest. Little data are available for the head-down condition. It appears that there is an acute fluid shift of 600-1000 ml from the legs within the first few hours of spaceflight which is quickly returned at recovery. A further reduction of 800 ml was measured over the next several days. Although the data are certainly incomplete, it appears that anti-orthostatic bed rest is associated with leg volume decrements between those of spaceflight and supine bed rest. A recent Soviet study (Anon, 1977) indicates that acute blood losses from the legs amounts to about 400 ml during head-down bed rest with a small additional loss over the next six weeks. Information such as this was very useful in accounting for the quantitatively different responses of bed rest and spaceflight. Loss in leg volume during periods beyond a week or so can be ascribed to further drying up of the legs as a result of: a) elastic forces approaching new equilibrium levels and influenced by devascularization and retoning, and b) loss of solid tissue, mostly muscle, due to disuse and deconditioning. Attempts should be made to independently measure the magnitude of tissue loss so that these components may be distinguished. It is worth mentioning that the concept that body fluid losses during spaceflight are primarily derived from leg fluid losses is supported by the Skylab experiments. Those studies reveal a loss of approximately 1.8 liters in leg volume at the end of several days in flight and this was associated with a total body water loss of nearly 1.5 liters (Hoffler, 1977; Leonard, 1977).

It is of interest to relate these leg volume changes that occur in hypogravity to those which occur during ordinary postural changes. Figure 9 is a simulation of short term postural change from the erect to supine position followed by an anti-orthostatic position ( $-4^{\circ}$ ) that continues for 48 hours. For the moment, consider the shorter-term maneuvers only. Leg volume measurements during acute postural changes or during lower body negative pressure studies suggest that about 400-600 ml blood are easily mobilized and transferred rapidly between legs and upper



**EFFECT OF SPACEFLIGHT AND BED REST ON TOTAL LEG VOLUME**

FIGURE 8



SIMULATION OF FLUID SHIFTS DURING ACUTE POSTURAL CHANGES

FOLLOWED BY BEDREST

FIGURE 9

body (Curve 1). In addition, there is another 500 ml or so of plasma that is normally pooled extravascularly in the leg tissues upon standing. Tilt studies suggest that this shift is essentially complete within 30 minutes, a behavior also shown by the simulation (Curve 2). This implies that in the erect posture about a liter of fluid is pooled in the two leg compartments (veins and interstitium) accompanied by an equivalent reduction in central blood volume (Curve 3), a  $\frac{1}{2}$  liter decrease in total blood volume (Curve 4) and about a 6% hemoconcentration (Curve 5). Tilting to a supine position returns fluid to the upper body and essentially reverses the previous changes. Thus, at least a liter of fluid is normally pooled in the legs when standing and is available to shift cephalad during hypogravity. However, the fluid shifts accompanying spaceflight are much larger than those indicated in Figure 8 associated with postural change.

The magnitude of this spaceflight shift and the extent to which the vascular, interstitial and perhaps intracellular compartments contribute is made difficult to resolve partly because of the uncertainty of the preflight or pre-bed rest reference leg volume measurement. This is indicated in the second half of the simulation of Figure 9 in which some suggested fluid changes during 48 hours of head-down bed rest are represented. If the reference position is taken as the upright state, the loss of nearly two liters of leg fluid (combined leg blood volume and tissue fluid) can be easily explained. Normally, the reference position is seldom mentioned in these studies. In the case of the spaceflight data previously shown, the reference position was not upright, but supine for about 30 minutes after ambulation. Thus, an unknown portion of previously pooled fluid was probably removed from the erect legs by the time the reference measurement was performed. This makes the changes observed in spaceflight even more dramatic compared to postural maneuvers (Gauer, 1976).

It is probable that the interstitial tissues in the legs contain a larger amount of readily mobilized fluid than was heretofore recognized under normal terrestrial surroundings. Assuming a total leg volume of 18 liters and accounting for calcified tissue and normal fractions of tissue fluid, it is possible to estimate a maximum leg interstitial fluid

component of about 2.5 liters. This may be the upper limit to be expected from this source. At this time, however, the precise contribution of each major fluid compartment to total leg volume changes is unknown.

Several other features of the anti-orthostatic simulation in Figure 8 should be noted. First, although almost a liter of leg fluid has shifted cephaled by two days, as measured from supine, central blood volume has returned to nearly normal, due to the reduction in total blood volume. Also, hemoconcentration occurs during both standing and, to a greater extent, during head-down bed rest. In the former case plasma is filtered into the leg compartments and body water is unchanged, while in the latter case plasma is lost primarily through the kidneys leading to a significant reduction in body water (curve 6).

It is imperative that leg fluid volume measurements performed in different studies have a common reference position because of the mobility of leg fluids and their postural dependency. It is recommended that measurements be performed first in the orthostatic position (i.e. quiet standing following a moderate ambulatory exercise) and then in the supine position at the end of 30 minutes. It is also recommended that subjects be well hydrated, but not overhydrated by ingesting a known quantity of water for the 24 hours prior to measurement.

#### B. Considerations in Venous Modeling

Consideration of the venous system must include its special properties such as collapse, valve action, and changes in pressure-volume relations of various venous segments such as those due to stress relaxation, venous tone, and external pressure. Special considerations for representing these properties are required when a model is used for simulating a wide range of stresses and operating conditions and where greater accuracy is required. Many existing models of venous segments are only designed to operate over a limited range of operating conditions and are, therefore, greatly simplified. A venous segment may be represented by the schematic elements shown in Figure 10.

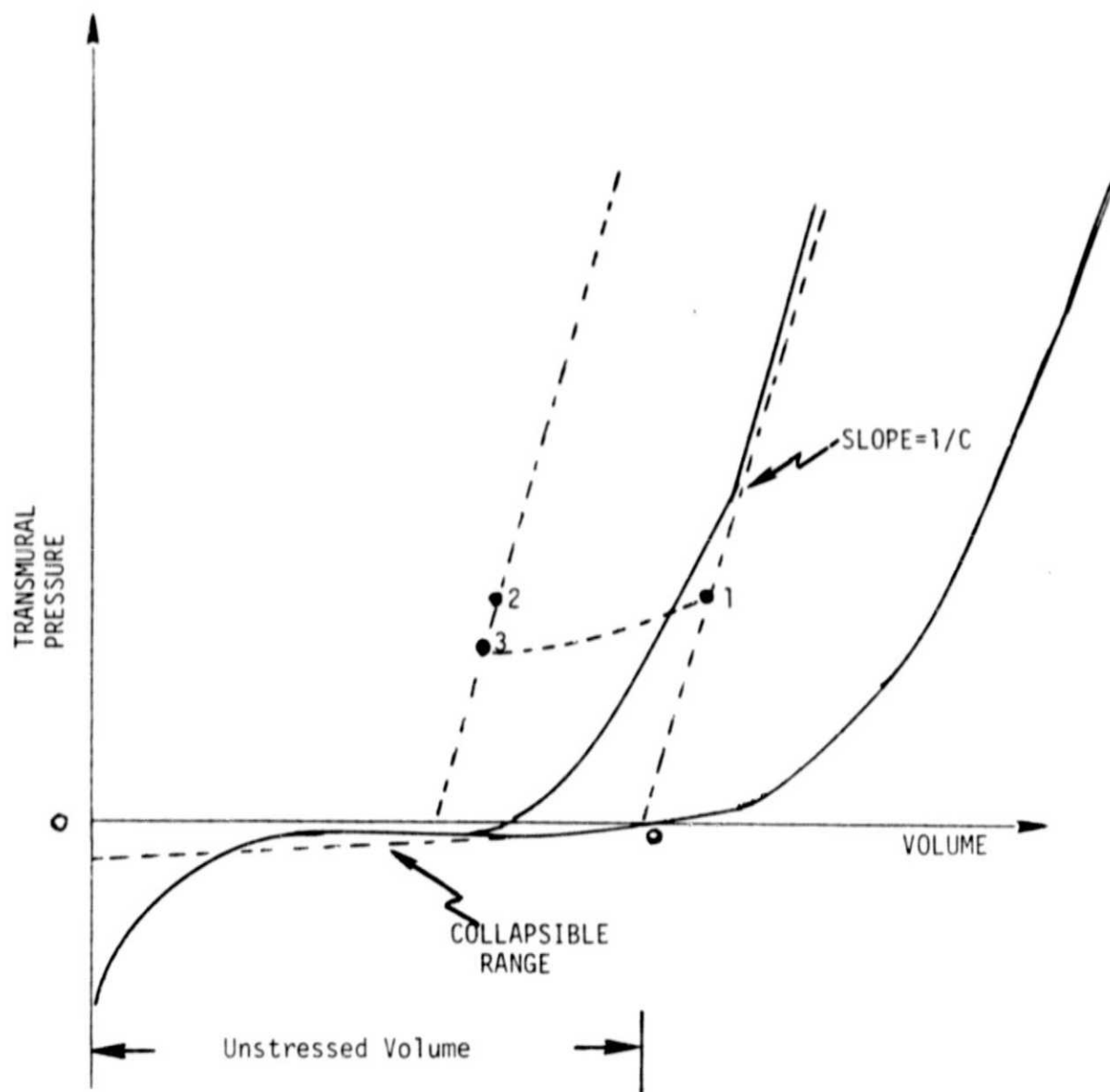


For the simplest case, the model parameters (resistance, compliance, and external pressure) which represent a particular segment of the venous circulation are constant. A constant compliance implies a linear pressure-volume relationship as indicated by the dashed line above the volume-axis in Figure 11 (the slope of the line is the inverse of compliance). The unstressed volume,  $V_0$ , is represented as the X-intercept of the pressure-volume curve. In the original formulation of the Guyton model, the collapsible range was represented by a horizontal line at zero transmural pressure. This formulation is sufficient for many applications of the model. However, this is not an adequate description of collapsible segments and does not permit the model to achieve a full range of unstressed volumes necessary for simulating head-down tilt. Accurate simulation over a wide range of operation requires variable quantities for all these elements. Changes in venous geometry requires a variable resistance, stress relaxation and nonlinearities in the pressure-volume relationship, and changes in body orientation in gravity requires changes in the pressure head in the segment.

In this study we are attempting to construct a model which accurately represents a wide range of stresses, with dynamic responses over acute and long range, and various orientations with respect to the gravity vector. In order to accomplish this with reasonable accuracy, direct experimental data should be obtained for these varying physiological parameters. Since little data are available many assumptions and simplifications are necessary in order to have a working model. Although the accuracy of the representation, and, therefore, the resulting predicted response, can be questioned in the absence of such data, a model of this type can be very useful when these limitations are understood. The following sections discuss these simplifications and assumptions with respect to the venous sections of the model.

### Compliance

Compliance is representative of the elastic property of the vein (elastance is the inverse of the compliance) and is the inverse of the slope



PRESSURE-VOLUME RELATIONSHIPS OF VEINS

FIGURE 11

of the pressure-volume curve. As can be seen from Figure 11, where a non-linear compliance is represented by a solid line (representative of data from Altman and Dittmer, 1971, for the venae cava), the linear assumption (dashed line) is adequate for the elastic range of high transmural pressures. Many changes in compliance can be represented with this linear assumption by shifting the line and changing its intercept with the volume axis ( $V_0$ ) which represents the unstressed volume (volume at zero transmural pressure) or by changing the external pressure which effectively shifts the curve up and down (by changing the pressure intercept) since transmural pressure equals the internal venous pressure minus the external pressure. Stress relaxation and devascularization can be represented by changing the unstressed volume,  $V_0$ , whereby the vein tends to restore the original pressure by retuning to accommodate the changed volume as shown in Figure 11 indicated by points 1 and 2. This, of course, assumes perfect and immediate stress relaxation. A more accurate representation is indicated by the course from point 1 to 3. In this case, the change in volume and pressure with respect to time is determined by assuming some time constant for the shift in  $V_0$  over time which allows only partial accommodation and a more accurate simulation with respect to time. A locus of these points would trace out a nonlinear compliance curve as represented by the data. This approach is only valid for the elastic range of the vein. There are limits to the range of volume changes that can be accommodated by the vein as indicated by the extremes of the curve. Intra-thoracic, intra-abdominal, and tissue pressure changes can be represented by changes in external pressure.

#### Venous Collapse

Venous collapse is assumed to occur when the volume in the segment becomes less than the unstressed volume (zero transmural pressure). The pressure inside the vein equals the pressure outside and the circular cross-section of the vein begins to become elliptical. In the collapsible region the volume changes drastically with little changes in pressure. A linear assumption during this range is shown in Figure 11 with the dashed line

below the volume axis. Snyder and Rideout (1969) have suggested that the slope in the collapsible range is such that the dashed line will intersect the pressure axis at -0.5 to -1.5 mm Hg for complete collapse. The effective compliance, in this case, turns out to be 20 times the compliance of the stressed region. Guyton and Adkins (1954) have measured the pressure in situ in the inferior venae cava of less than 1 mm Hg transmural pressure during collapse. Under any circumstances, little error is involved in this region if the slope allows most of the unstressed volume to be lost for slightly negative transmural pressures.

A change in resistance also results from change in cross-sectional geometry of the vein. Snyder and Rideout (1969) present a mathematical development of this resistance term, by assuming an elliptical cross section for volumes less than the unstressed volume,  $V_0$ . Resistance is given as the inverse of the first term on the right side of the following equation

$$\Delta P = \frac{9 \mu \pi^2 L^2 R^2}{2 \rho q^3} F$$

for fully developed non-pulsatile flow (neglecting inertance terms) where

$F$  = flow

$q$  = instantaneous volume ( $q < V_0$ )

$\mu$  = viscosity of fluid

$R$  = radius when  $q = V_0$

$\rho$  = density of fluid

This equation represents a nonlinear effect of flow because of the effect of pressure on volume. It can be seen that for a working fluid and a segment of tube with constant properties that the resistance to flow is inversely proportional to the instantaneous volume of the segment to the third power (Resistance  $\propto \mu/q^3$ ). Although a preliminary version of this modeling approach has been attempted, some parameter estimation will be needed to represent lumped values for the entire segment of the leg veins.

An increase in resistance with collapse can also be represented implicitly by a decreasing pressure drop for flow. This effect can be modeled by replacing the single slope assumed for the collapsible region

by two or three different segments with increasing slope as venous segment volume approaches zero. This is suggested by the data of Altman and Dittmer (1971) for the very nonlinear portion of the solid line in the collapsible range of Figure 11. This mechanism has also been implemented and investigated. Although volume shifts were adequately simulated, it is less certain whether local venous circulation was appropriate. Flow changes in leg elements have not been well described for long term bed rest.

An additional and possibly complementary approach would describe the effects of venous collapse with more explicit dependence of the external pressure. The analysis, based on the work of Permutt and Riley (1968) varies from the previous one in that the pressure-flow relationships of a "waterfall" are used rather than Poiseuille's law. In this model the veins are completely collapsed at any point where transmural pressure approaches zero. The waterfall effect can be described as a system where flow is independent of the pressure drop across the ends of the tube or a change in flow has no effect on the pressure drop. In the venous circulation this occurs when the downstream pressure is less than the external pressure and a portion of the segment is collapsed. In this case, the driving pressure for flow is the inflow pressure (post capillary pressure) minus the external pressure. Flow exists whenever the pressure in the vessel rises above the external pressure; whenever transmural pressure becomes zero or below the vein collapses. The resulting cessation of flow causes pressure to rise and the vessel opens. By this action the vessel automatically adjusts its cross sectional area and, therefore, its resistance to flow such that the outflow pressure at the point of collapse is only very slightly above the external pressure.

This modeling approach would appear to offer a solution for computing the pressures and volumes of a collapsible segment which is dependent on external pressures and post capillary pressures. This would likely resolve some current problems encountered with the model at the more extreme tilt angles and improve its stability.

#### Venous Tone Changes

Venomotor tone control effects refer to the active constriction or dilation of venules caused by variations of arterial pressure, particularly

at the carotid sinus, mediated through the sympathetic nervous system. These effects can be included rather simply by varying the unstressed volume (equivalent to shifting the pressure-volume curve in Figure 11 to the right or left) in a manner based upon experiments reported by Alexander (1964). Of course, this approach is not valid at the elastic extremes of the vein. For simulations in this range, variable functional relationships for venous tone changes would be required similar to that suggested by Snyder (1969).

#### Fluid Storage in Upper Body Veins

Large veins above the heart are known to partially collapse upon standing and these could conceivably act as a large depot for blood storage during zero-g or anti-orthostatic maneuvers without proportional increases in blood pressures. (Any additional volume beyond the zone of free distensibility contributes toward increasing venous pressures and presumably would initiate renal mechanisms which act to reduce the excess stressed volume.) Adaptive mechanisms may exist which can increase the unstressed volume capacity of upper body veins and accommodate excess fluids. These influences include stress relaxation, vascularization (i.e., increases in number of capillaries), and altered volume receptor sensitivity. No information is available regarding these factors during hypogravic stress. Veins in regions above the heart are not normally subjected to venous pressure increases of more than small magnitudes. To what extent the pulmonary vessels also accommodate blood beyond their normal storage capacity is an unanswered question, albeit an important one for obvious clinical reasons.

The model at present does not contain a separate vascular compartment above the heart level and, therefore, does not exhibit collapsed veins in the erect position nor refilling and fluid storage during hypogravity and anti-orthostasis. The acute central circulatory hypervolemia which occurs at zero-g onset is eventually self-correcting by action of blood volume receptors. Likewise, the early expansion of the upper body interstitial compartments reverses itself due to autoregulation of capillary pressure and enhanced lymph flow. There is little quantitative data to support or refute this model prediction, although it does appear to be at odds

with the well known subjective reports of head fullness, head tissue puffiness and neck vein distention during prolonged hypogravity either by spaceflight or head-down bed rest. Also, in a recent study by the Soviets, it was reported that an excess volume of at least 300 ml was found in the vasculature of the head and chest after 45 days of head-down bed rest (Anon, 1978). Interstitial fluid volume changes have not been reported for these body regions.

It appears then that the model may have to be altered in some manner to reproduce these effects. Adaptation of volume receptors does occur in the model, but other physical factors are able to take over their function. Also, blood volume corrections are completed before the longer term stress relaxation influences become operative. The most feasible approach is the addition of collapsible veins in a separate cephalad compartment.

#### Venous Compliance During Prolonged Zero-g

The Lower Body Negative Pressure tests conducted during Skylab provides some clues regarding dynamic changes of effective venous compliance during prolonged weightlessness. LBNP creates a pressure gradient for fluid pooling in the veins and perhaps tissues of the lower half of the body. The volume of blood diverted is a significant factor in the degree of stress produced. Leg volume measurements showed that the amount of blood pooled in the legs during inflight LBNP was considerably greater than preflight or postflight LBNP. Since this phenomena was most apparent during the first few minutes of LBNP, the most plausible explanation is a relatively empty venous system in the legs at the beginning of the test (Johnson, et al, 1977).

Veins require only low transmural pressures to retain their circular configuration. Under conditions of lower pressure they tend to become elliptical or flat. In this state, relatively large volumes of blood could be accommodated before any change in venous pressure occurred. Thus, the amount of fluid initially present in this region of high compliance would influence the total amount of blood drawn from the central circulation and thereby affect the cardiovascular response. A similar argument may be made for the pressure-volume relationship in the tissue. The larger residual volume at the end of the LBNP recovery period that occurred inflight may reflect a greater outflow during lower body negative pressure of fluid from capillaries into tissues. It may also indicate that the operating range of the pressure-volume relationship in the veins has shifted to the zone of high compliance.

Prolonged spaceflight may act to increase compliance of the veins, reduce tone of supporting muscle in proximity to the veins and diminish tissue pressure, all of which may enhance the leg fluid pooling during LBNP or upon orthostasis during recovery. In addition to these effects, other long term influences such as reverse stress relaxation (which will partially restore the pressure in the leg veins) and/or devascularization of the tissues (which accomplishes the same thing by reducing capillary capacity) may occur and act to reduce blood pooling. The totality of these effects may explain the fact that the greatest instability and orthostatic intolerance was noted during the first three weeks of flight while after 5-7 weeks cardiovascular response became more stable and evidence of improved orthostatic tolerance appeared. Two other effects that may have aided the partial recovery of inflight tolerance are the influence of fluid stored in the upper body during zero-g which may be available during LBNP stress and a gradual increase in baroreceptor sensitivity may have occurred resulting in more intense vasoconstriction and venomotor function during LBNP.

A summary of these hypotheses are shown in Figure 12. We are presently using model simulation (using the short term pulsatile cardiovascular model as adapted to LBNP and tilt) to evaluate and test these hypotheses using spaceflight and ground-based data for comparison. While the study is not yet complete we have determined that the greatest contributing factor to the orthostatic intolerance of spaceflight LBNP is the decrements of blood volume (approximately 500 ml). The inflight heart rate response to maximal LBNP ( $-50$  mm Hg) can be compared to 1-g LBNP with a 15% hemorrhage. On the other hand, no support was found for a simple passive increase in leg venous compliance to explain the LBNP response. The increased leg volume pooling during LBNP (compared to preflight) can be primarily explained by the partial collapse of leg veins and a reduced leg blood volume during rest. Accordingly we would expect that the reverse stress relaxation mechanism would have a significant effect in restoring orthostatic tolerance in the model. Whether or not this would be true in the human subject is an unanswered question. These and the other hypotheses are currently under consideration from both a theoretical and experimental approach.

#### C. Transcapillary Fluid Movement During Hypogravic Stress

##### Hypothesis Development and Model Simulation

Capillary exchange of fluids is a highly dynamic process capable of moving large volumes of fluid very rapidly in either direction between capillaries and surrounding tissue. We have already discussed the importance of this mechanism in initiating the acute stress stage of weightlessness. The current configuration of the leg filtration mechanisms in the computer model is shown in Figure 13. The rate and direction of the transcapillary fluid shift is determined by the relation between the hydrostatic and colloid osmotic pressure gradient across the capillary walls and the functional properties of the capillary membrane. Changes in capillary hydrostatic pressure and in the capillary surface area are subject to

ZERO-G HYPOTHESES DERIVED FROM LOWER BODY NEGATIVE PRESSURE  
STUDIES AND MODEL SIMULATIONS

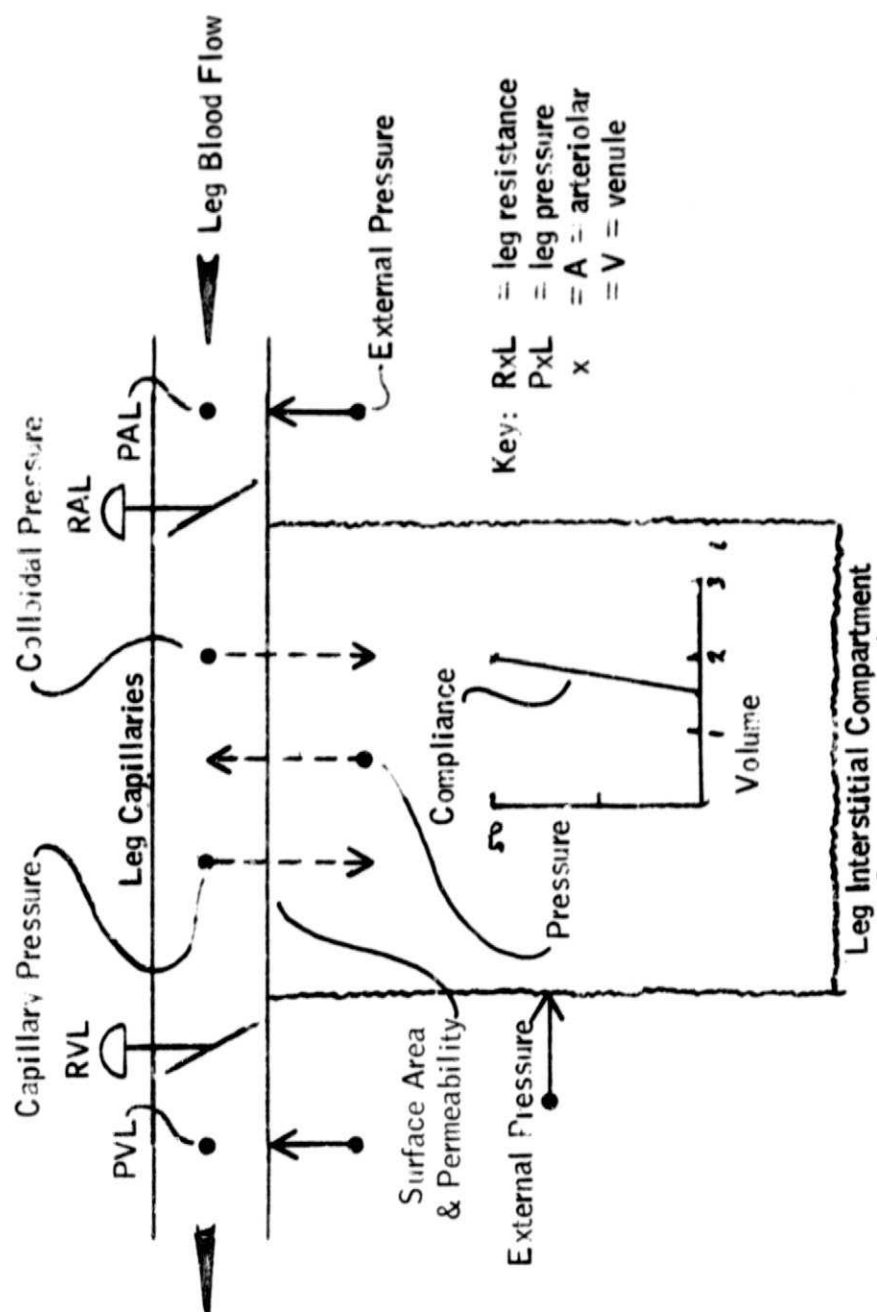
A. Zero-G Effects That Diminish Orthostatic Tolerance

- Leg veins are partially collapsed during rest in zero-g
- Total blood volume is reduced
- Compliance of veins increases
- Tone of supporting muscle is reduced
- Tissue pressure surrounding veins is reduced

B. Zero-G Effects That Aid or Restore Orthostatic Tolerance

- Excess fluid storage in upper body at rest may be available during LBNP
- Increased baroreceptor and volume receptor sensitivity enhances venomotor and vasoconstrictor function
- Reverse stress relaxation reduces zone of free distensibility

FIGURE 12

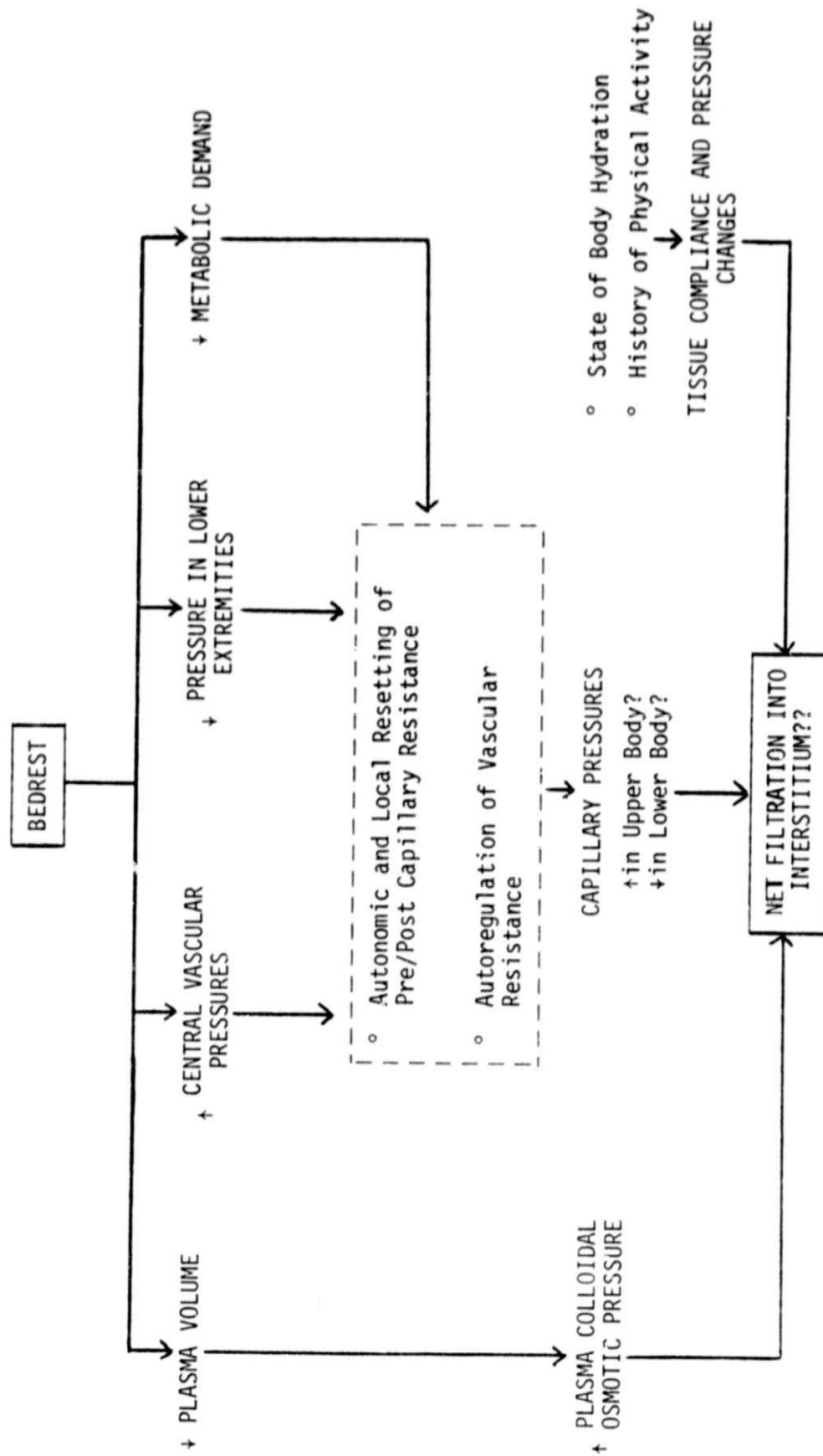


SCHEMATIC OF LEG FILTRATION MECHANISMS

FIGURE 13

substantial variations by way of shifts in the pre- and postcapillary resistances. Tissue fluid pressure, determined by the elastic characteristics of the tissue and its state of hydration, acts to oppose capillary pressure. Reflex control of the partition of fluid between the intra- and extravascular fluid compartments is accomplished by the capability of the pre-/postcapillary resistance ratio to vary dramatically, particularly in the muscle tissues. An increased pre-/postcapillary resistance ratio correspondingly lowers mean capillary pressure. Whenever capillary pressure is decreased, the Starling filtration equilibrium is disturbed to favor filtration from the tissues into the circulation and vice versa.

During standing capillary pressures in the feet will increase by 75-85 mm Hg. While as much as 500 ml plasma may filter into the tissues within 30 minutes, this effect is limited by the opposing tissue pressure, a reflex reduction in capillary surface area, and by concentration of plasma colloids which are not easily filterable. Little is known about the reverse situation of head-down tilt. Figure 14 summarizes some of these factors which may influence transcapillary filtration in both upper and lower body during anti-orthostatic bed rest. Decreased volume pooling in the veins of the legs tends to reduce local venous pressure and in turn pressures on the venous side of the local capillary bed, a condition which promotes the transfer of interstitial fluid into the capillaries. The opposite effect presumably influences the capillaries in the upper body, at least transiently. Alterations in pre-/post capillary resistance ratio may be predicted by several central and local mechanisms responding to pressure and flow disturbances. As plasma is lost through the kidneys, the colloidal osmotic pressure increases and opposes the blood hydrostatic pressure effect. Finally, tissue pressure will change in proportion to the tissue fluid gained or lost as well as due to functional states of hydration and activity. Variations in tissue compliance may also be expected during hypogravic disturbances. As this diagram suggests, it is



FACTORS CONTROLLING PLASMA INTERSTITIAL FILTRATION DURING ANTI-ORTHOSTATIC BEDREST

FIGURE 14

not easy to predict the time course and eventual net change in total body interstitial fluid in the entire body. Spaceflight and bed rest data reveal no clear cut trend in this regard. These studies have revealed that more realistic simulations can be achieved by improving the description of the differential behavior of upper and lower body capillary filtration and the factors which influence this process.

The Guyton model now contains separate capillary beds each associated with the leg circulation or the upper body circulation. The leg resistance elements (both pre- and post-capillary) are at present modeled in a very similar fashion as these in the upper body. They both account for passive distention and collapse, autonomic influence, angiotensin, vasoconstriction, and viscosity effects. However, there are undoubtedly some fundamental differences between the lower and upper body resistance capacitance and capillary elements. This has become more apparent during these simulation studies of orthostatic and anti-orthostatic stresses. The possibility exists that leg vessels can sustain high pressures (as in 1-g orthostasis) more easily than the upper body vasculature. Mechanisms which are currently under consideration for inclusion in the lower extremity elements include those due to: a) locally produced vasoconstriction (myogenic), b) enhanced autonomic effects, and c) chemical effects (i.e. catecholamines). Many of these effects become significant only during prolonged postural changes and have not been adequately investigated.

A simulation of events in the legs during anti-orthostatic bed rest is shown in Figure 15. Our analyses suggest that at  $-4^{\circ}$  leg capillary pressures decrease only about 5 mm Hg as measured from supine, compared to a 50-60 mm Hg change in the erect position. As one may suspect, this suggests a much slower dynamic response during a slight head-down tilt than during a more severe headup tilt. In addition to the decrease in capillary pressure, the model simulation reveals alterations in plasma colloidal pressure, tissue pressure and pre- and postcapillary resistances. Transfer of fluid inward towards the circulation during hypogravity would

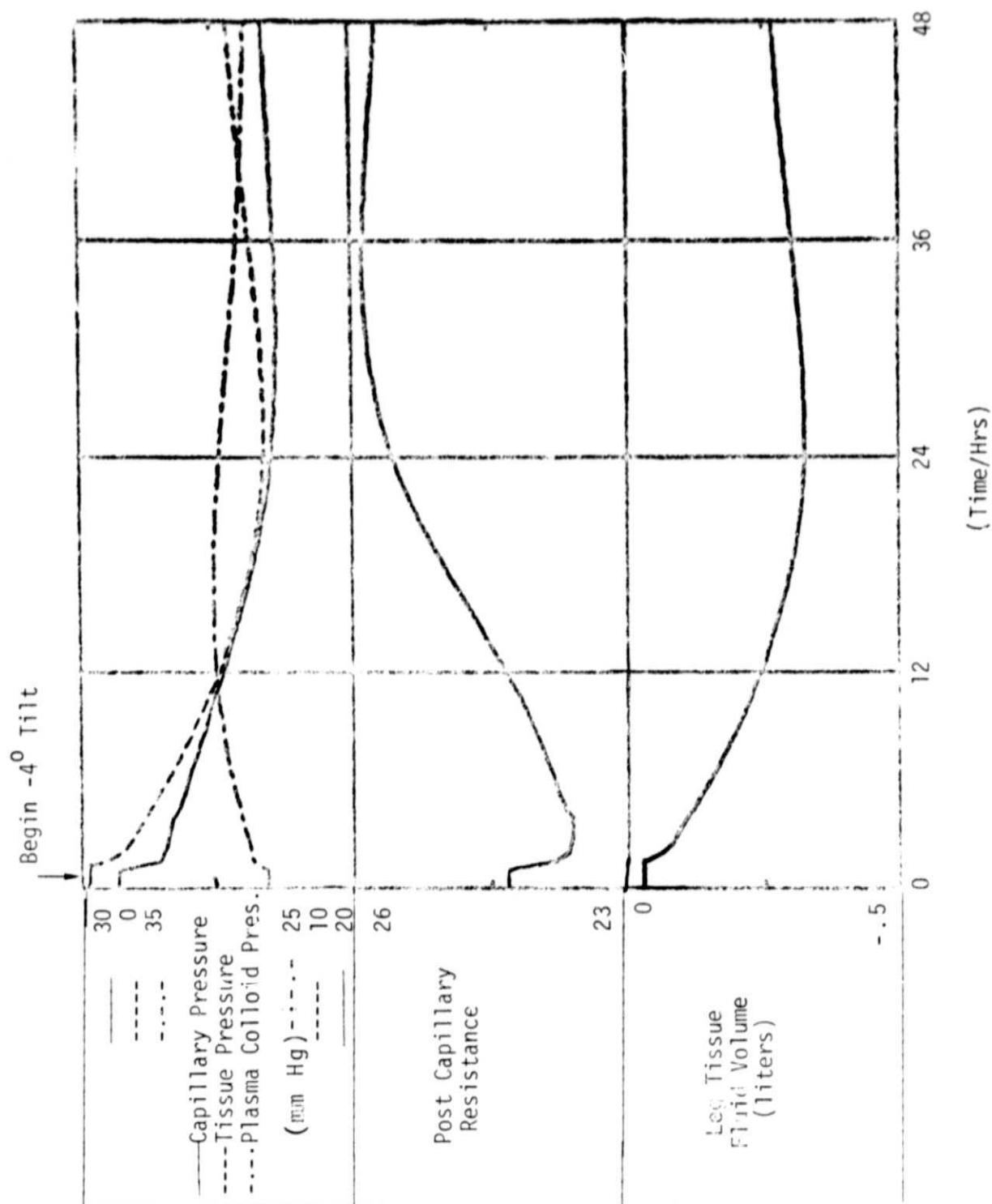


FIGURE 15

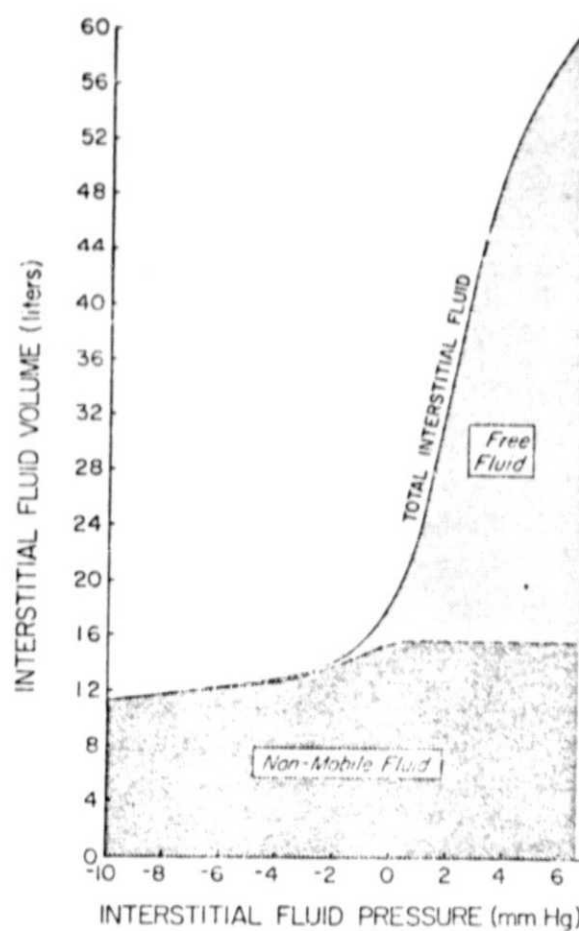
PARAMETERS INFLUENCING LEG TRANSCAPILLARY FILTRATION  
DURING ANTIORTHOSTATIC BED REST

be expected to continue until the tissue pressures declined and a balance of Starling transcapillary forces was again achieved. The model presently predicts the resulting tissue fluid losses over 24 hours in the  $-4^{\circ}$  position to be nearly equivalent to that gained by the tissues in 30 minutes of standing. Experimental data suggests that prolonged periods of anti-orthostatic bed rest may favor even larger leg fluid decrements. If this is true, the model will require the addition of adaptive elements that favor long term drying up of the legs. These would include adjustments of vascular resistance and capacitance as well as those which influence tissue compliance. It is these latter effects on tissue compliance which we would now like to consider.

#### Pressure-Volume Relationship of the Tissues

To perform any type of quantitative analysis of interstitial fluid dynamics, it is essential to know the relationship between pressure and volume in the interstitial spaces. Guyton has presented a composite diagram showing the relationship of interstitial fluid pressure to total interstitial fluid volume, including the relationship between free fluid and non-mobile fluid in the interstitium (see Figure 16 ). The solid curve represents the relationship between interstitial fluid pressure and total interstitial fluid volume.

According to experimental observation, normal interstitial fluid is in the negative pressure range. Normal tissues, therefore, have essentially zero free fluid (only small, mainly collapsed channels of fluid along tissue membranes and fibers). However, as soon as the interstitial fluid pressure rises into the positive pressure range, large quantities of free fluid begin to appear. At this point the volume expansion of the interstitium is associated with a relatively smaller change in tissue pressures than in the case where tissue pressures are normally negative. We believe this nonlinear compliance of the tissues is significant to the quantitative understanding and simulation of weightlessness and the terrestrial experimental analogs of weightlessness.



(From Guyton et al., *Physiol. Rev.* 51:527, 1971.)

ESTIMATED TISSUE PRESSURE-VOLUME RELATIONSHIP  
OF ENTIRE HUMAN BODY

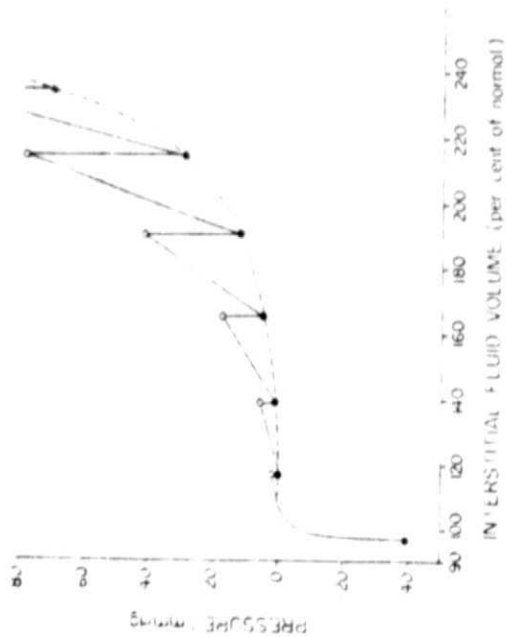
FIGURE 16

During postural changes, between supine and standing, a large quantity of free tissue fluid is mobilized and the region of interest may be in the positive pressure range when compliances are relatively high. On the other hand, during head-down tilt or prolonged weightlessness when tissues are dehydrated, the relationship between fluid volume and pressure may be altered insofar as little if any free fluid is present and tissue compliances are much lower. In our simulation studies, we have in fact found that in order to achieve the proper degree of leg tissue dehydration during head-down tilt, it was necessary to alter tissue leg tissue compliance several fold compared to the simulation of standing. As we have shown the model at present does not include a nonlinear compliance relationship in the leg tissues, although the upper body tissues do contain this feature. The data from which Figure 16 was derived were extrapolated from the dog to the entire body of the human. While it is probable that similar relationships hold for the leg tissues, the precise quantitative description may not be the same as that shown here. We have already discussed that in weightlessness, much more fluid is derived from the leg tissues than can be accounted for from data on simple postural changes. A more complete description of the leg tissue pressure-volume relationship may assist in understanding this phenomena.

#### Stress-Relaxation of the Tissue Spaces

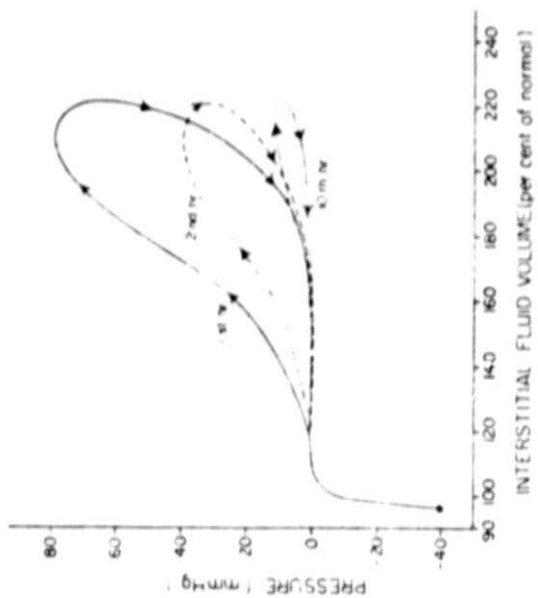
It appears that the tissues are not entirely elastic structures because they exhibit the phenomenon of stress-relaxation (i.e. delayed compliance) in the same manner as do blood vessels and many other tissues in the body. If the volume of fluid in the tissue space is increased suddenly the pressure rises very rapidly at first, but then decays back toward a lower level, even though the interstitial fluid volume is maintained at exactly the same elevated volume. (See Figure 17(a)). Stress-relaxation is a dynamic phenomena since its effect increases with time. This is illustrated in Figure 17(b), in which fluid was forced in and out of the subcutaneous tissue spaces in a sinusoidal manner with a cycle period of approximately one hour. These hysteresis curves illustrate that

(A)



Results from a typical experiment in which the interstitial fluid volume was expanded in six rapid steps, with each expansion phase requiring 2 minutes and each period of test between expansion phases 6 minutes. This figure shows that during rapid expansion the pressure rises markedly (to the open circles) and then falls, because of stress relaxation during the period of no expansion, to lower values (to the solid circles).

(B)



Approximate hysteresis curves of subcutaneous tissue as estimated from experiments such as those illustrated in Figure 6-8 and experiments on reabsorption of edema fluid (Ref: Guyton, et al., *Physiology and Control of Fluids*, Saunders Co., Philadelphia, 1975)

# INFLUENCE OF STRESS RELAXATION ON TISSUE FLUID VOLUME - PRESSURE RELATIONSHIP

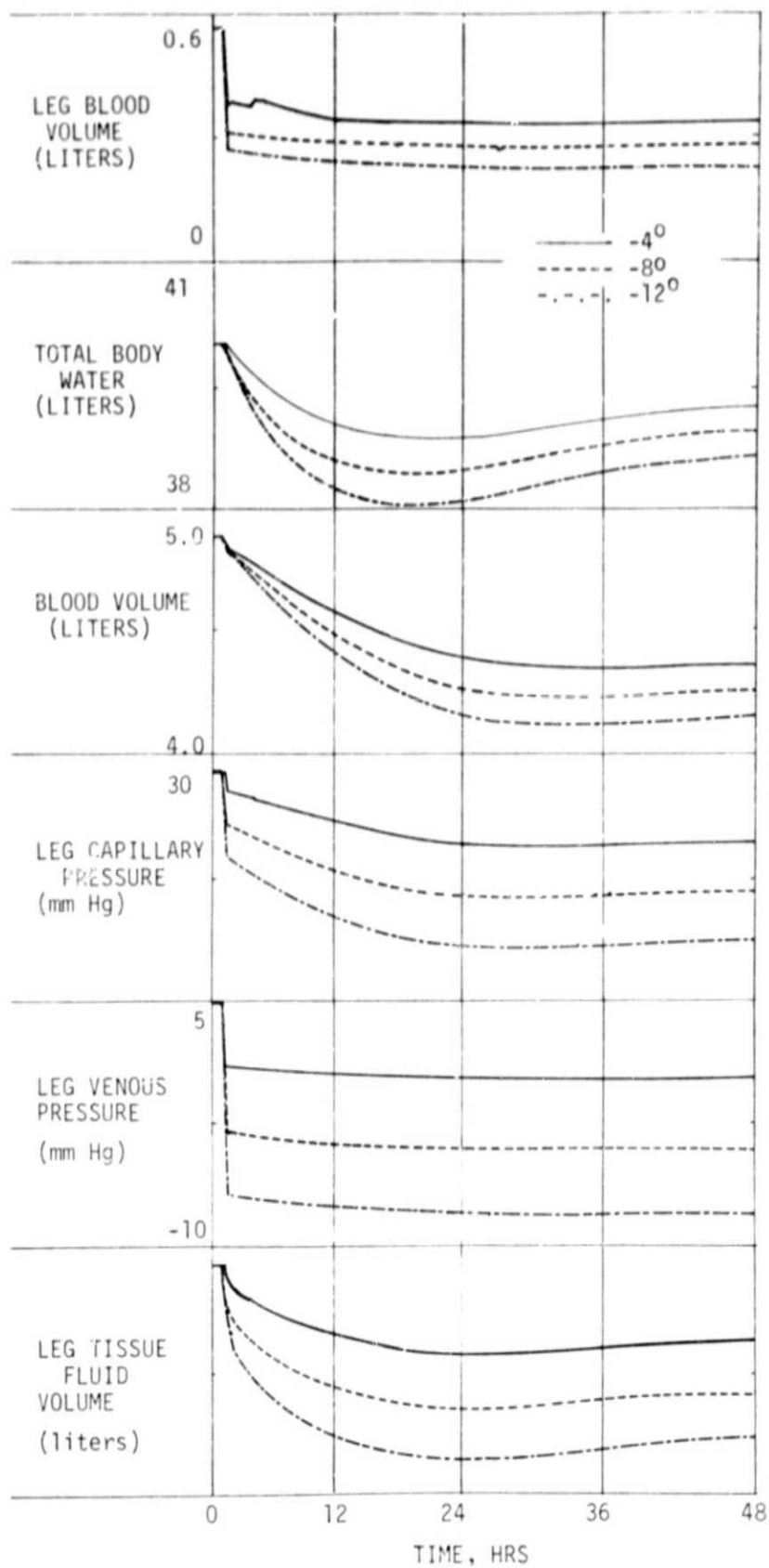
FIGURE 17

the previous history of volume expansion has a great effect on the instantaneous compliance value. Based on this data, one may expect that a greater degree of fluid from leg tissues may be lost during head-down bed rest from subjects who have been previously ambulatory or standing for long periods of time or who are well hydrated. The inclusion of a stress-relaxation function in the model would provide an additional mechanism for longer term depletion of leg fluid separate from the effects of muscle atrophy. In this case, reverse stress relaxation may be hypothesized.

#### D. Sensitivity Analysis of Anti-Orthostatic Bed Rest Simulations

The most promising candidate approaches for modeling the leg elements were implemented and tested at various angles of head-down tilt similar to those used experimentally. The results of a series of simulations at -4, -8, and -12 degrees tilt are shown in Figure 18. The objective of this sensitivity analysis was to test the model's ability to respond appropriately to head-down tilt and to demonstrate that increasing the angle of tilt increases the severity of leg fluid shifts. There is insufficient information available to validate the accuracy of each response, so that these predictions should be considered only preliminary. Since the manner in which the legs are modeled will influence the amount of total fluid shifted from the legs, these predictions will presumably be modified when more realistic leg elements are added.

As the angle of tilt increases, the effect on shifting fluids from the interstitium is proportionately greater than the shift of leg blood. This may be expected in that most of the fluid from the leg vasculature drains out for only small negative angles, similar to the effect seen during LBNP when the greatest amount of leg pooling occurs during the lowest pressure differentials. Capillary pressures decrease in accord with the negative hydrostatic gradient imposed. In these runs between 600 and 1200 ml fluid have shifted from the legs and this is reflected



SENSITIVITY ANALYSIS OF ANTI-ORTHOSTATIC SIMULATION:  
INFLUENCE OF TILT ANGLE

FIGURE 18

in the loss of total body water at the end of two days. In previous simulations of supine bed rest the blood volume changes were nearly equivalent to the losses of blood from the legs. These anti-orthostatic simulations, by contrast, indicate that blood volume losses are always greater than that shifted from the legs. This condition arises because of an excess hydrostatic pressure at the volume receptors which is maintained throughout negative tilt, a situation not previously encountered in the supine position. It may be expected that a similar phenomena would occur in human subjects.

#### E. Toward a More Appropriate Simulation of Weightlessness

Our early hypogravic simulation studies were concerned with demonstrating that an appropriate fluid shift from the lower extremities could explain important short and long term responses. Fluid redistribution was initiated by producing the appropriate magnitudes and direction of fluid movement in a rather artificial manner. The studies summarized herein have been our first attempt to model the primary physical forces that create the driving force for these fluid shifts. Weightless space flight and the terrestrial analogs of zero-g such as water immersion, supine bed rest and anti-orthostatic bed rest can each be characterized and distinguished in part by the degree and time course of headward fluid movement. While the elastic forces of the body tissues, both intravascularly and extravascularly are involved in fluid redistribution for all these stresses, the external forces acting on the body are somewhat different in each situation. For example,

<u>Hypogravic State</u>	<u>External Forces</u>
Water Immersion	External pressure gradient equal to blood hydrostatic gradient
Supine Bed Rest	Partial removal of erect gravity gradient
Head-down Bed Rest	Removal and partial reversal of gravity gradient
Spaceflight	Complete removal of gravity gradient in all body positions.

Ideally, we desire to simulate each of these conditions by using model elements which more closely correspond to the internal and external forces of the real system. In the present simulation of anti-orthostatic bed rest the most significant external force is the altered gravity vector and its effect on the hydrostatic column of blood. This study, by introducing these forces in an explicit manner, represents an important advance in achieving more realistic simulations of hypogravity states.

We recognize, however, that one of the major characteristics of weightlessness and its experimental analogs is the departure from the 1-g ambulatory state which includes powerful mechanisms for maintaining orthostasis. Our present model is initialized in the supine position and does not contain all the mechanisms which are representative of ambulatory man. We have speculated that if a model could be constructed which contains the ability to simulate an upright active position, the simulation of bed rest or weightlessness could be initiated by simply removing the gravity vector. The hypothesis that would be tested is that the hypogravic state, if chronically maintained, would lead to gradual removal or readaptation of those mechanisms which have been developed to protect man from orthostatic collapse. Thus, we would be able to reproduce the same effects we have already achieved using a more appropriate method to reverse leg fluid pooling, and in addition we could examine the so-called "deconditioning effects" characteristic of prolonged hypogravity. We have already approached this problem by distinguishing between the cardiovascular properties of physically trained and untrained man and incorporating these into another of our models - a short term closed circulation system which simulates exercise, LBNP and tilt.

It is not expected to be an easy matter to construct a model which can be initialized in the ambulatory state. An upright reference position would really represent a composite of positions (standing, sitting, reclining) and activity levels (sedentary to strenuous exercise). It may be argued that an upright steady-state condition does not really exist in man, just as we are finding that alteration of human function continues during

prolonged periods of bed rest. While a simulation such as the one described would more truly integrate the combination of mechanisms operative in hypogravity and assist in relating the various experimental maneuvers now being utilized to study weightlessness, it is questionable whether there is sufficient information available for its implementation. Nevertheless, it may be useful to consider that the study of weightlessness can be approached by examining long term anti-orthostatic as well as orthostatic positions.

## CONCLUSIONS

Our main emphasis in this study was modification of the Guyton model to include the capability of head-down tilt. This has been accomplished and results for short term bed rest have been presented. Future plans will include formulating more accurate descriptions of leg elements and adding adaptive mechanisms as necessary. Our objective will be to improve the realism of the work already accomplished and to add a predictive capability for long term anti-orthostatic bed rest. This objective includes the accurate comparison between supine bed rest and anti-orthostatic bed rest using computer models. Our specific recommendations for improving these simulations are summarized in Table 2. All of these aspects have been previously discussed in this paper. Much of this work will depend upon experimental results which are not yet realized. For this reason, we have also summarized some of the most significant experimental objectives which would assist in generating this information (see Table 3). Much of these data can be obtained during future bed rest studies and more basic studies on tissue and circulatory behavior will also be required.

Although this study has emphasized the influence of fluid shifts as the main determinate of the bed rest response, we realize that other factors are important to more fully understand the effects of bed rest induced hypogravity. Some of these other factors are shown in Table 4 along with the known influence that these have had on our previous simulations of supine bed rest. It is an advantage of the simulation approach that these hypotheses can be easily tested both individually and in combination. In this preliminary study of anti-orthostatic bed rest simulation the systems analysis approach has once again proved its usefulness by identifying important mechanisms, identifying systems which need further experimental description and in assisting in the development of a general hypothesis.

TABLE 2

## RECOMMENDATIONS FOR IMPROVING SIMULATION OF HEAD-DOWN BED REST

- o MORE ACCURATE DESCRIPTION OF COLLAPSIBLE VEINS IN UPPER AND LOWER BODY
- o POSSIBLE ADDITION OF HEAD COMPARTMENT TO PERMIT COLLAPSIBLE VEINS ABOVE HEART TO REFILL AND STORE FLUIDS DURING HYPOGRAVITY
- o MORE ACCURATE DESCRIPTION OF DIFFERENCES BETWEEN TRANSCAPILLARY FILTRATION IN UPPER AND LOWER BODY
- o MORE ACCURATE DESCRIPTION OF DIFFERENCES BETWEEN CAPILLARY AND RESISTIVE FLOW ELEMENTS OF UPPER AND LOWER BODY
- o MORE ACCURATE DESCRIPTION OF CONTROL OF VENOUS CAPACITY AND COMPLIANCE DURING SHORT TERM (NEUROGENIC) AND LONG TERM (HORMONAL, TONUS OF SURROUNDING TISSUES, STRESS RELAXATION) STRESS
- o INFLUENCE OF NON-FLUID RELATED "DECONDITIONING" ON CIRCULATORY CONTROL
- o ACHIEVEMENT OF A REFERENCE AMBULATORY POSITION

TABLE 3

EXPERIMENTAL OBJECTIVES IDENTIFIED BY SIMULATION ANALYSIS:  
FLUID VOLUME DYNAMICS DURING HYPOGRAVITY

BED REST EXPERIMENTS

- o TIME COURSE AND DEGREE TO WHICH VASCULATURE, INTERSTITIUM AND INTRACELLULAR FLUID SHIFTS CONTRIBUTE TO LOSS OF LEG VOLUME.
- o CHANGES IN LEG VENOUS PRESSURES AND BLOOD FLOW DURING ACUTE AND ADAPTIVE PHASE
- o DEGREE OF FLUID STORAGE IN UPPER CIRCULATION AND INTERSTITIUM DURING ACUTE AND CHRONIC STRESS STAGES OF HYPOGRAVITY
- o DYNAMICS OF LEG BLOOD AND LEG TISSUE FLUID REFILLING DURING, BEFORE, AND AFTER ORTHOSTASIS
- o COMPARE LEG VOLUME FLUID SHIFTS TO LOSSES OF BLOOD VOLUME AND TOTAL BODY WATER

OTHER EXPERIMENTS (ANIMAL?)

- o ALTERATIONS IN PRE- AND POST-CAPILLARY RESISTIVE ELEMENTS IN LEGS (DURING REDUCED PRESSURE)
- o ACTIVE (NEURAL AND HORMONAL) AND PASSIVE (CHANGES IN SURROUNDING TISSUES, STRESS RELAXATION) CHANGES IN BLOOD CAPACITANCE ELEMENTS OF LEGS
- o PRESSURE VOLUME RELATIONSHIPS OF LEG VEINS DURING THE COLLAPSED STATE AND OF LEG TISSUE SPACES DURING DEHYDRATION; POSSIBLE INFLUENCE OF REVERSE STRESS RELAXATION; DYNAMICS OF COMPLIANCE CHANGES DURING PROLONGED HYPOGRAVIC STRESS

TABLE 4

## FACTORS TO CONSIDER IN ANTI-ORTHOSTATIC BEDREST SIMULATION

<u>FACTORS</u>	<u>SIMULATION EFFECTS</u>
1. Longitudinal angle of body with respect to gravity vector	1. Reduces or reverses hydrostatic pooling of fluid in legs, induces central hypervolemia and results in loss of fluids and electrolytes
2. A) State of hydration: relative fluid intake during bedrest compared to controls	2. Altered fluid and salt intake will effect magnitude of natriuresis, diuresis, steady state renal output, changes in body fluid composition, plasma levels of renin-angiotensin aldosterone and ADH
B) Electrolyte balance: relative salt intake during bedrest compared to controls	
3. Altered muscle tissue function:	
A) Depressed daily metabolic rate	3. Loss of intracellular fluids and electrolytes; reduction in blood flow, tissue fluid and plasma volume
B) Degradation due to disuse atrophy	
4. Depressed sweat losses	4. Accounts for increased renal output often observed during prolonged bedrest.

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